NEW DRUG APPROVAL

Brand Name	Apretude
Generic Name	cabotegravir
Drug Manufacturer	ViiV Healthcare

New Drug Approval

FDA Approval Date: December 20, 2021

Review Designation: Priority

Type of Review: Type 5 - New Formulation or New Manufacturer; New Drug Application (NDA): 215499

Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Human Immunodeficiency Virus (HIV) initiates infection by fusing its envelope membrane with the cell membrane through a process which is triggered through interactions with the cellular receptor and coreceptor. While the mechanism of HIV fusion has been extensively studied, the point of its entry into cells remains controversial. HIV has long been thought to fuse directly with the cell plasma membrane. However, several lines of evidence suggest that endocytic entry of HIV can lead to infection and, moreover, that endocytosis could be the predominant HIV entry pathway into different cell types.

Exposure to human immunodeficiency virus (HIV) can be a consequence of many of the risk-taking behaviors that occur among adolescents. There are unique challenges to the prevention, diagnosis, and treatment of HIV infection among adolescents. A comprehensive program for adolescents at risk for HIV infection must include efforts at preventing infection (such as outreach programs and access to pre- and postexposure prophylaxis), easily accessible testing, risk reduction counseling, and behavioral health services. Education and prevention efforts must take into account the developmental level of the patient, as well as social and psychological variables. Programs that have been successful are youth-friendly, peer-oriented, inclusive of sexual and gender minorities, and targeted toward specific high-risk behaviors, offering a range of services through multidisciplinary teams.

In 2019, there were an estimated 1.7 million adolescents aged 10 to 19 living with HIV worldwide.

In the United States, youth aged 13 to 24 years accounted for an estimated 21 percent of all new HIV infections in 2018. The majority of HIV-infected adolescents and young adults acquired HIV through sexual activity. Young men who have sex with men accounted for 82 percent of new HIV infections in males in this age group. Black youth accounted for an estimated 52 percent of all new infections, followed by Hispanic/Latino (25 percent) and White (18 percent) youth.

In the United States, by the end of 2015, approximately 1.1 million people of all ages were living with HIV, with an estimated 10,000 individuals being classified as having become infected perinatally. These patients are rarely diagnosed in adolescence, but they make up a sizable proportion of youth living with HIV in the United States.

Efficacy

Clinical Trials in Adults for HIV-1 Pre-Exposure Prophylaxis

The safety and efficacy of Apretude to reduce the risk of acquiring HIV-1 infection were evaluated in 2 randomized, double-blind, controlled, multinational trials, HPTN 083 in HIV-1 uninfected men and transgender women who have

sex with men and have evidence of high-risk behavior for HIV-1 infection and HPTN 084 in HIV-1 uninfected cisgender women at risk of acquiring HIV-1.

Participants randomized to receive Apretude initiated oral lead-in dosing with 1 oral cabotegravir 30-mg tablet and a placebo daily for up to 5 weeks, followed by Apretude 600-mg (3-mL) intramuscular injection at months 1 and 2 and every 2 months thereafter and a daily placebo tablet. Participants randomized to receive Truvada initiated oral Truvada (TDF 300 mg/FTC 200 mg) and placebo daily for up to 5 weeks, followed by oral Truvada daily and placebo intramuscular injection at months 1 and 2 and every 2 months thereafter.

Trial 201738 (HPTN 083 [NCT02720094])

In HPTN 083, a non-inferiority study, 4,566 cisgender men and transgender women who have sex with men were randomized 1:1 and received either Apretude (n = 2,281) or Truvada (n = 2,285) as blinded study medication up to Week 153.

At baseline, the median age of participants was 26 years, 12% were transgender women, 72% were non-White, and 67% were younger than 30 years. The primary endpoint was the rate of incident HIV-1 infections among participants randomized to daily oral cabotegravir and intramuscular injections of Apretude every 2 months compared with daily oral Truvada (corrected for early stopping). The primary analysis demonstrated the superiority of Apretude compared with Truvada with a 66% reduction in the risk of acquiring HIV-1 infection, hazard ratio (95% CI) 0.34 (0.18, 0.62); further testing revealed 1 of the infections on Apretude to be prevalent then yielding a 69% reduction in the risk of HIV-1 incident infection relative to Truvada.

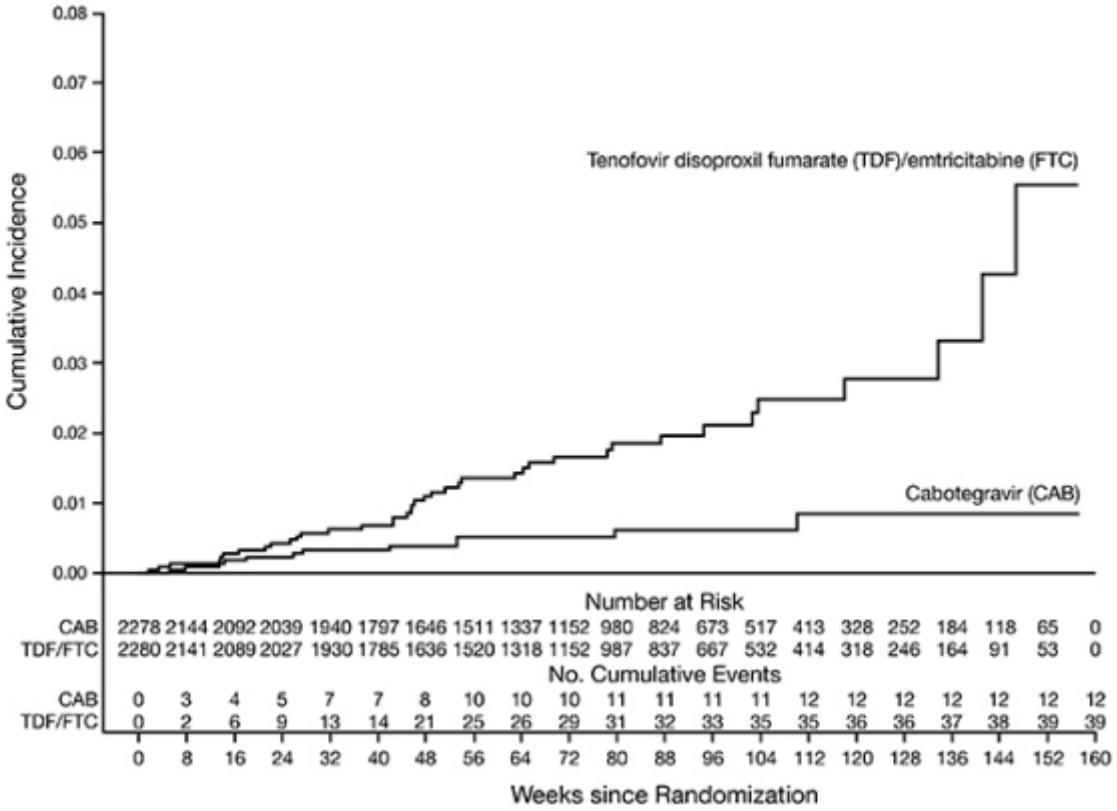
Table 1. HIV-1 Infection Results During Randomized Phase in HPTN 083: Extended Retrospective Virologic Testing with Readjudicated Endpoints

	APRETUDE (N = 2,278)	TRUVADA (N = 2,281)	Superiority *P* Value
Person-years	3,211	3,193	
HIV-1 infections (incidence rate per 100 person-years)	12[b] (0.37)	39 (1.22)	
Hazard ratio (95% CI)	0.31 (0.16, 0.58)		0.0003

[a] mITT from Supplemental Virology Report.

[b] Following the primary analysis, extended retrospective virologic testing was performed to better characterize the timing of HIV-1 infections. As a result, 1 of the 13 HIV-1 incident infections in participants receiving APRETUDE was determined to be a prevalent infection. The original hazard ratio (95% CI) from the primary analysis is 0.34 (0.18, 0.62).

Figure 1. Cumulative Incidence of HIV-1 Infections in HPTN 083



Results from all subgroup analyses were consistent with the overall protective effect. A lower rate of incident HIV-1 infections was observed for participants randomized to Apretude compared with participants randomized to Truvada.

In the HPTN 083 clinical trial, an increased incidence of pyrexia (including pyrexia, feeling hot, chills, influenza-like illness) (4%) was reported by participants receiving Apretude compared with participants receiving Truvada (<1%). Vasovagal or pre-syncopal reactions considered treatment related were reported in HPTN 083.

Trial 201739 (HPTN 084 [NCT03164564])

In HPTN 084, a superiority study, 3,224 cisgender women were randomized 1:1 and received either Apretude (n = 1,614) or Truvada (n = 1,610) as blinded study medication up to Week 153.

At baseline, the median age of participants was 25 years, >99% were non-White, >99% were cisgender women, and 49% were < 25 years of age.

The primary endpoint was the rate of incident HIV-1 infections among participants randomized to oral cabotegravir and injections of Apretude compared with oral Truvada (corrected for early stopping). The primary analysis demonstrated the superiority of Apretude compared with Truvada with an 88% reduction in the risk of acquiring incident HIV-1 infection, hazard ratio (95% CI) 0.12 (0.05, 0.31); further testing revealed 1 of the infections on Apretude to be prevalent then yielding a 90% reduction in the risk of HIV-1 incident infection relative to Truvada.

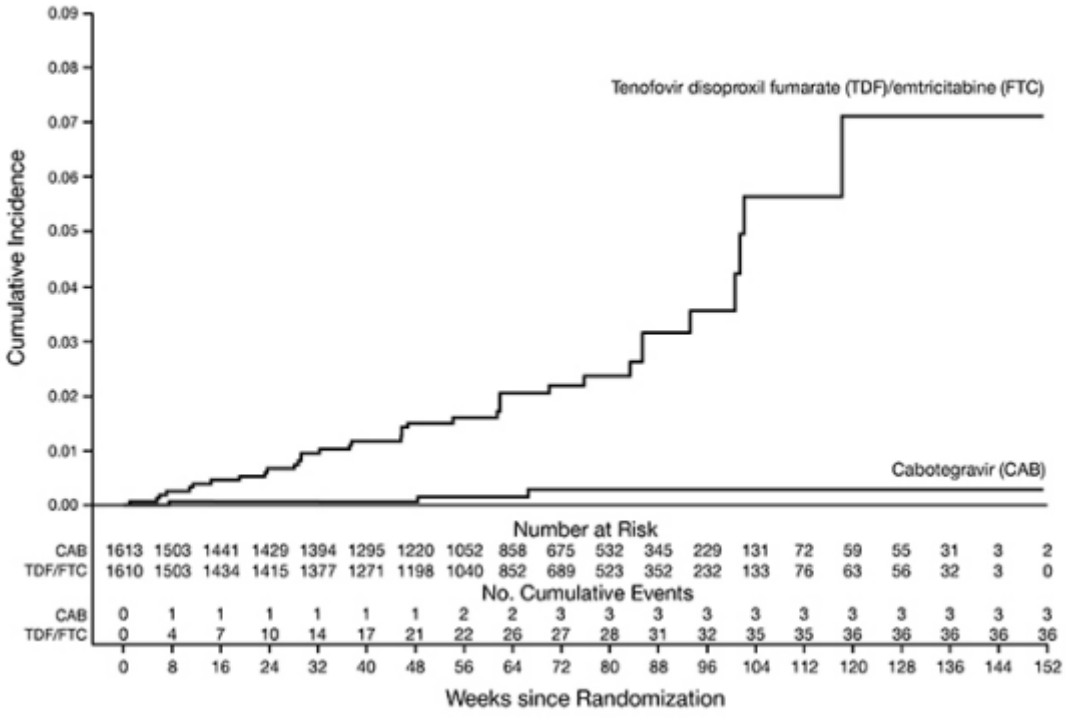
Table 2. HIV-1 Infection Results during Randomized Phase in HPTN 084: Extended Retrospective Virologic Testing with Readjudicated Endpoints

	APRETUDE (N = 1,613)	TRUVADA (N = 1,610)	Superiority *P* Value
Person-years	1,960	1,946	
HIV-1 incident infections (incidence rate per 100 person-years)	3[b] (0.15)	36 (1.85)	
Hazard ratio (95% CI)	0.10 (0.04, 0.27)		<0.0001

[a] mITT from Supplemental Virology Report.

[b] Following the primary analysis, extended retrospective virologic testing was performed to better characterize the timing of HIV-1 infections. As a result, 1 of the 4 HIV-1 incident infections in participants receiving APRETUDE was determined to be a prevalent infection. The original hazard ratio (95% CI) from the primary analysis is 0.12 (0.05, 0.31).

Figure 2. Cumulative Incidence of HIV-1 Infections in HPTN 084



Results from pre-planned subgroup analyses were consistent with the overall protective effect. A lower rate of incident HIV-1 infections was observed for participants randomized to Apretude compared with participants randomized to Truvada

The most commonly reported adverse event (all causality) leading to discontinuation was increased alanine aminotransferase (1%) with Apretude and Truvada. The side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trials.

Safety

ADVERSE EVENTS

The most common adverse reactions (all grades) observed in at least 1% of subjects receiving Apretude were injection site reactions, diarrhea, headache, pyrexia, fatigue, sleep disorders, nausea, dizziness, flatulence, abdominal pain, vomiting, myalgia, rash, decreased appetite, somnolence, back pain, and upper respiratory tract infection.

WARNINGS & PRECAUTIONS

- Comprehensive management to reduce the risk of HIV-1 acquisition.
- Potential risk of developing resistance to Apretude if an individual acquires HIV-1 either before or while taking Apretude or following discontinuation of Apretude. Reassess risk of HIV-1 acquisition and test before each injection to confirm HIV-1 negative status.
- Residual concentrations of cabotegravir may remain in the systemic circulation of individuals up to 12 months or longer.
- Hypersensitivity reactions have been reported in association with other integrase inhibitors. Discontinue Apretude immediately if signs or symptoms of hypersensitivity reactions develop.
- Hepatotoxicity has been reported in patients receiving cabotegravir Clinical and laboratory monitoring should be considered. Discontinue Apretude if hepatotoxicity is suspected.
- Depressive disorders have been reported with Apretude. Prompt evaluation is recommended for depressive symptoms.

CONTRAINDICATIONS

- Unknown or positive HIV-1 status.
- Previous hypersensitivity reaction to cabotegravir.
- Coadministration with drugs where significant decreases in cabotegravir plasma concentrations may occur.

Clinical Pharmacology

MECHANISMS OF ACTION

Cabotegravir is an HIV-1 antiretroviral drug in a long-acting formulation. Cabotegravir inhibits HIV integrase by binding to the integrase active site. This binding of cabotegravir prevents insertion of unintegrated linear viral DNA into the host DNA by strand transfer, which is essential for HIV replication.

Dose & Administration

ADULTS

HIV infection, treatment: Oral:
Oral lead-in: 30 mg once daily, in combination with oral rilpivirine, for ~1 month (≥28 days) prior to initiation of cabotegravir and rilpivirine injections, to assess tolerability to cabotegravir. **Note:** Final oral dose should be taken on the same day as initiation of injections.
Oral bridging therapy: 30 mg once daily, in combination with oral rilpivirine, in patients who plan to miss a scheduled cabotegravir and rilpivirine injection visit by >7 days. **Note:** First oral dose should be taken ~1 month after the last injection dose and continued until the day injection dosing is restarted. Oral therapy may be used to replace up to 2 consecutive missed monthly injection visits.
Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

PEDIATRICS

Safety and efficacy have not been established in pediatric patients.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustment necessary.

HEPATIC IMPAIRMENT

No dosage adjustment necessary.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: Single-dose vial of 600 mg/3 mL (200 mg/mL) of cabotegravir extended-release injectable suspension.